Assessment of the validity of pap smear cytology in diagnosing cervical intraepithelial neoplasia in the maternity teaching hospital in Erbil city

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Baran Kamal Barzanji *

Abstract

Background and objectives: Cervical smears can reduce both incidence and mortality rates from invasive cervical cancer. Despite its success, cervical cytology has important limitations. The aim of this study is to assess the validity of conventional Pap smear in diagnosis of cervical intraepithelial neoplasia in Erbil through comparison with colposcopy with or without cervical biopsy.

Methods: A hospital-based study was carried out in Erbil Maternity Hospital from the 1st May to 31st December 2008. The study sample included 336 women attending the breast disease center for routine breast examination. Cervical Pap smear followed by colposcopic examination was done for each woman on the same day. Cervical punch biopsy was taken for those with abnormal colposcopic findings. Colposcopy with or without biopsy was considered as a gold standard diagnosis of cervical intraepithelial neoplasia (CIN).

Results: : Out of 336 women, 48 (14.3%) had abnormal cervical smear results, of which 43 (12.8%) of the total had low-grade cervical lesions and 5 (1.5%) of the total had high-grade cervical lesions. Colposcopy-directed biopsy revealed that 69 (20.5%) had abnormal findings of which 65 (19.3%) women had CIN I and 4 (1.2%) of the total had CIN II and III. The sensitivity and specificity of the cervical smear were 62.3% and 98.1%, respectively. The positive predictive value was 89.6% while the negative predictive value was 91%. The false negative percentage was 37.7%. The accuracy of the test was 90.8% and the degree of agreement between Pap smear and colposcopy with biopsy results was 90.2%.

Conclusion: The high accuracy of cervical smear in this study and high agreement rate between cervical cytology and colposcopy indicates that conventional Pap smear is an important dependable screening test in spite of its low validity in terms of its sensitivity.

Key words: Cervical intraepithelial neoplasia, Pap smear, Validity, Erbil.

Introduction

Cervical cancer is the second most common female cancer in the world that affects some 489000 women and kills 268000 women each year all over the world. It is the commonest cause of female cancer deaths in South-East Asia, Africa and other parts of the developing world [1, 2]. It accounts for 15% of all female cancers in developing countries[3]. The predominant risk factor for cervical cancer is persistent infection with human papilloma virus (HPV) which is now well established. Other high risk factors are early sexual intercourse, multiple sexual partners and cigarette smoking[4]. Unlike most other cancers,

***Department of Community Medicine, College of Medicine, Hawler Medical University, Erbil, Iraq.**

cervical cancer can be prevented through screening programs, designed to identify and treat the precancerous lesions. One of the screening programs is Pap smears (cervical cytology). Population screening with annual cervical Pap smears after beginning of sexual activity until the age of 35 and at 5 year intervals after that can reduce both incidence and mortality rate from invasive cervical cancer[3,4]. Other screening program is visual inspection of cervix after application of lugol's iodine or acetic acid. Due to the operational difficulties of Pap smear, this method could be a more feasible alternative screening method in low resource countries[5]. Despite its success in identification of benign, premalignant and malignant conditions, cervical cytology has some limitations, as false-negative cytology results[6]. If a woman has an abnormal Pap smear that suggests the presence of cervical intra-epithelial neoplasia (CIN), colposcopy should be performed to detect areas with abnormal colposcopic pictures which require cervical biopsy[7]. Cervical cancer screening program have been established in Erbil during 2006. Nowadays the program covers three primary health care centers and the Maternity Teaching Hospital. All abnormal Pap smears are referred to the colposcopy unit of the Maternity Teaching Hospital for confirmation of the findings and management. As there is no formal evaluation of the cervical cancer screening program and its role in cervical cancer prevention has not been assessed, this study aimed to assess the validity of conventional Pap smear in Erbil city through comparison with colposcopy with or without colposcopy-directed cervical biopsy.

Methods

A hospital-based cross sectional study was carried out at the Maternity Teaching Hospital in Erbil city from May to December 2008. The convenient sample taken included all married women who were attending the breast disease center for routine breast examination during that period; they had sexual relationship at least for one year duration and subjected to Pap smear examination for the first time, while the study sample excluded unmarried females, menopause females & those for whom Pap smear test had been done previously. Verbal consent was obtained from all women. The smears collected between 10^{th} and 20^{th} day of the menstrual cycle using Ayer's spatula by rotating it 360 degrees around transformation zone after cleaning the area from secretions by a piece of dry cotton. The woman should not have received any vaginal treatment or douches 48 hours prior to the smear. Although colposcopy with or without biopsy was considered as a gold standard[2], all women, were subjected to both Pap smear and colposcopy with or without biopsy on the same day. Colposcopy directed punch biopsies were taken for those who had abnormal colposcopy findings. Women who had satisfactory colposcopy with no suspicious lesions were defined as normal and this was accepted as a truly negative outcome. All colposcopic examinations and biopsies were carried out by the researcher. All Pap smears and biopsy examinations were conducted by the same histopathologist. The researcher and histopathologist were masked with respect to the screening test results.

The Bethesda classification system of the Pap smear was used where cytological abnormalities classified as low grade squamous intra-epithelial lesion (LSIL) which is synonym of the terminology mild dysplasia or CIN I in which the abnormality is confined to 1/3 of the cervical squamous epithelium and the cytological changes are nuclear enlargement, multinucleation, hyperchromasia with thin cytoplasm and perinuclear holo, in addition to the koilocytotic atypia, while high grade squamous intra epithelial lesion (HSIL) is synonym of the terminology moderate and severe dysplasia with cervical carcinoma insitu comprising CINII (approximately two thirds of cervical squamous epithelium involvement) and CINIII (more than two thirds

to a full thickness of cervical squamous epithelium involvement without involvement of basement membrane). The histopathological abnormalities was classified as CIN I, CIN II, and CIN III [8, 9]. The differences and agreements of the findings in the two methods were assessed thoroughly. Agreement rate estimated as = sum of all symmetrical results (both positive and negative) when both tests are applied / total sampleX100. Validity of Pap smear was estimated by measuring sensitivity and specificity of the test in which : Sensitivity = true positive / total positive X 100 and specificity = true negatives /total negative X 100. True positives are those who have abnormal findings by both Pap smear and colposcopy with biopsy, and true negatives are those who have normal results by both Pap smear and colposcopy. Total positives consist of all abnormal findings diagnosed by colposcopy and biopsy, and total negatives consist of all normal colposcopic results. False positives are persons who do not have the disease but abnormal Pap smear result, and false positive % = 1- specificity, while false negatives are patients who actually have the cervical abnormality but normal Pap smear results, and false negative% = 1- sensitivity. Predictive value of Pap smear test is measured by determining positive and negative predictive values.

Positive predictive value= true positives/ test positive X100

Negative predictive value= true negatives/ test negatives X100

Accuracy of Pap smear test = true positive + true negative/ total sample X100[(10)]

Statistical analysis was conducted using Microsoft excel and Mc Nemar test was used as a statistical test and the P value of less than 0.05 regarded as a level of significant.

Results

The study sample comprised 336 women, their ages ranged between 20-45 years, with a mean age± SD of 32.8±8.3 years.

Out of them, 48 (14.3%) had abnormal Pap smear results, 43 (12.8% of the total) had low-grade lesion and 5 (1.5% of the total) had high-grade lesion. Colposcopic examination and biopsy showed that 69 (20.5%) had abnormal findings, 65 of them (19.3% of the total) had CIN I and 4 (1.2%of the total) had CIN II &III (Table 1).

Table1. Pap smears and colposcopy directed biopsy findings among screening population.

Classification of findings	Pap smear		Colposcopy and biopsy	
	No.	%	No.	%
Normal	288	85.7	267	79.5
Abnormal				
Abnormal LSIL (CIN I)	43	12.8	65	19.3
Abnormal HSIL (CIN II and CIN III)	5	1.5	4	1.2
Total	336	100	336	100

Colposcopy and biopsy results of the 48 women who had abnormal Pap smears, revealed that only 43 of them had abnormal findings (true positive), and 5 of them (10.4%) had normal findings with false positive percentage of 1.9%, while colposcopy examination of the 288 women who had normal Pap smears, revealed that 262 of them are true negatives, and 26 (9%) of them had abnormal findings (24 of them had CIN I and 2 had CIN II) with false negative percentage of 37.7%. The sensitivity of Pap smear was 62.3% while the specificity was 98.1%. The positive predictive value (PPV) was 89.6% while the negative predictive value (NPV) was 91.1%. Accuracy of the test was 90.8% (Table 2).

Table 2: Pap smear results in comparison with colposcopy and biopsy.

Pap smear	**Colposcopy and biopsy**		
	Positive	Negative	Total
Positive	43	5	48
Negative	26	262	288
Total	69	267	336

P value <0.01

Colposcopic examination of the 43 women with LSIL on Pap smear, showed agreement with Pap smear findings in 39 cases whereas 4 cases were completely normal (with false positive% of 9.3%). Out of the 5 cases diagnosed as HSIL by Pap smear, colposcopy and biopsy revealed that 2 cases had CIN I and another 2 cases had CIN II while one case was normal (with false positive% of 20%). The agreement rate of Pap smear and colposcopy findings was 90.2%.These findings are shown in (Table 3).

Table 3: A comparison between Pap smear and colposcopy directed biopsy for screened women.

Pap smear	**Colposcopy and biopsy**			
	Normal	LSIL (CIN I)	HSIL (CINII and CIN III)	Total
Normal	262	24	2	288
LSIL	4	39	0	43
HSIL	1	2	2	5
Total	267	65	4	336

P value <0.01

Discussion

In this study Pap smear underestimated the population with LSIL in the total sample in comparison with colposcopy (12.8% versus 19.3%), which is reflected in the low proportion of detection of abnormal findings in general (14.3% versus 20.5%), although there was overestimation of HSIL (1.5% versus 1.2%). These differences indicate that Pap smear in this setting tends to be less efficient in detecting low-grade lesions; a finding which has been also reported in other settings from different contexts[11]. The proportion of abnormal Pap smear findings revealed by this study (14.3%) coincided with that revealed by a study done in India (15%) [12]. The proportion of LSIL (12.8%) and HSIL (1.5%) was higher than that reported by Pap smear in US (2.4% and 0.6% respectively)[13]. The proportion of abnormal findings revealed by colposcopy and biopsy (20.5%) is higher than that reported in a study carried out in 5 sub-Saharan African countries (15%) [14]. Despite the demonstrated ability of cervical cytological screening in reducing cervical cancer mortality, conventional Pap test is less sensitive than it is generally believed to be[15]. The sensitivity of Pap smear test obtained in this study is relatively low (62.3%), but it is within sensitivity range revealed by similar studies done in India, Africa, US and France (44 - 72%) [2, 15, 16], while the reported specificity is high (98.1%) which agrees with the findings of studies done in India, Africa, and France (94 -98%)[2,16]. Decision makers should take in consideration these findings highlighting the low Pap test sensitivity when establishing health policies[11]. The low sensitivity of a single Pap test makes it necessary to screen women relatively frequently-every three to five years[15]. Despite its success, cervical cytology has important limitations, as false-negative results being the most important[6]. The false-negative rate in this study (37.7%) is higher than that reported by other studies

in UK (15-35%) [17], which is a reflection of its low sensitivity rate (62.3%). These false negative results have important medical, financial and legal implications; they are a leading cause of medical malpractice litigation in western countries[6]. In fact, false-negative cytology specimens are significant because cervical intraepithelial neoplasia or more invasive lesions may escape detection and progress to more advanced disease during the period between tests [18, 19]. Minimizing errors in cytology remains a challenge for cervical smear test. This could be achieved through improvement of the quality of sample taking (using liquid-based Pap test), slide processing and overall diagnostic performance of cervical cytology [6, 8]. The American College of Obstetricians and Gynecologists and American Society for Colposcopy and Cervical Pathology have recommended the use of HPV testing in addition to the Pap smear in all women over the age of 30 to improve the sensitivity and to decrease the false-negative rate of the screening test[17]. In this study the rate of false positive LSIL was 9.3%. A study in Birmingham showed nearly 19% of women with minor cytological abnormalities had no visible lesion[20]. The potential adverse effects of false-positive results include patient anxiety regarding the risk of cervical cancer [18, 19], as well as the unnecessary inconvenience, discomfort, and expense of follow-up diagnostic procedures. Studies have shown that distribution of educational materials to patients that explain the meaning of abnormal results is associated with a reduction in patient anxiety and stress and a better patient understanding of test results[21]. As Pap smear underestimated the abnormal findings in comparison with colposcopy and biopsy in this study, potentially various combinations of cytology and colposcopy may be used to generate screening protocols that might result in more effective screening as recommended by other workers[22]. However, colposcopy has little role as a screening tool for cervical cancer on a population basis because of the requirement of a high degree of technical expertise, instrumentation and time required for an adequate examination whereas cervical smears can be used to screen far greater numbers of people in the same time. In this study the accuracy of Pap smear, which is the test ability to correctly identify positive and negative cases [23], is considered high (90.8%). The accuracy of the Pap test is strongly affected by disease prevalence; higher disease prevalence is associated with higher estimates of sensitivity and lower estimates of specificity (with a greater effect on specificity)[11]. Even though the results of cervical cytology and colposcopy in this study as well as many other studies are usually highly correlated, some caution is warranted in the interpretation of observed accuracy measures, since a certain degree of a gold standard misclassification cannot be excluded in colposcopy [2], and the need to improve the specificity of colposcopic-guided biopsy remains [24].

Conclusion

The high accuracy of cervical smear in this study and high agreement rate between cervical cytology and colposcopy indicates that conventional Pap smear is still an important dependable screening test in spite of its low validity in terms of it's sensitivity.

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